PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 13/00, 33/15 | A1

(11) International Publication Number: WO 96/28717

(43) International Publication Date: 19 September 1996 (19.09.96)

(21) International Application Number: PCT/GB96/00493

(22) International Filing Date: 4 March 1996 (04.03.96)

(30) Priority Data:
9504893.0 10 March 1995 (10.03.95) GB

(71) Applicant *(for all designated States except US)*: CORTECS LIMITED [GB/GB]; The Old Blue School, Lower Square, Isleworth, Middlesex TW7 6RL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BARNWELL, Stephen, George [GB/GB]; 30 Alun Crescent, Chester CH4 8HN (GB). BURNS, Stephen, John [GB/GB]; Cortecs Limited, Research & Development Division, Techbase 1, Newtech Square, Deeside Industrial Park, Deeside, Clwyd CH5 2NT (GB). HIGGINBOTTOM, Simon [GB/GB]; 4 Scotton Avenue, Little Sutton, South Wirral L66 4TJ (GB).

(74) Agents: CHAPMAN, Paul, William et al.; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB).

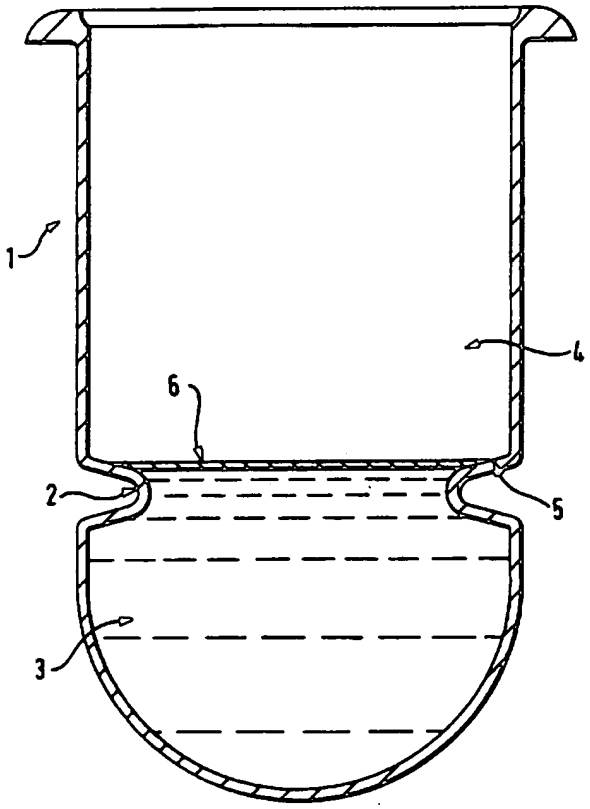
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TESTING VESSEL

(57) Abstract

A dissolution testing vessel comprising means which prevent a formulation undergoing dissolution testing from floating freely at the surface of the testing medium, but which do not prevent the testing medium from moving freely within the vessel. In particular, the means consists of a mesh or grille.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

TESTING VESSEL

This invention relates to a dissolution testing vessel, and in particular to a vessel for testing dissolution of pharmaceutical formulations, particularly buoyant pharmaceutical formulations.

In the field of pharmaceutical formulations there exists a need to study the behaviour of the formulations *in vitro* in such a way that the *in vivo* behaviour of the formulations can be predicted. Many different types of formulation are produced, for example, slow-release formulations which are designed to release active ingredient(s) over a given period of time at an approximately constant rate.

Other formulations may be designed to release an initial "burst" of active ingredient followed by a steady-state release thereafter. For these various types of formulation, a reliable method of assessing dissolution *in vivo* and consequently analysing the rate of release of active ingredient(s) is required.

WO-A-9206680 is an example of an application relating to novel pharmaceutical formulations. In that disclosure dissolution testing is carried out using a method based upon the USP XXII dissolution test for tablets and capsules. This test is designed to subject the samples to an environment similar to that found in the intestine.

In that test a dissolution apparatus is used, again as specified by USP XXII. This essentially consists of a dissolution vessel into which is placed a buffered medium in which the dissolution testing of the pharmaceutical

formulation will be carried out. The sample is simply "dropped" into the medium and is allowed to float freely at the surface. The body of the medium is agitated by means of a paddle which is rotated. Paddle height is adjusted so that the top edge of the blade is level with the surface of the liquid. Then, at various time points throughout the test, aliquots of the dissolution medium can be removed and replaced with fresh buffer. These aliquots can then be tested to determine the amount of active ingredient(s) released from the sample formulation. This method is described in detail by Burns *et al, Int. J. Pharmaceutics* (1995) (in press).

There is, however, a problem with this adaptation of a traditional type testing method, in that since the sample can float freely at the surface of the liquid it can in fact be caught up by the paddle and indeed the formulation under test could even stick to the paddle. Clearly, this may result in a delay in the breakdown of the formulation, and hence release of active ingredient(s), by virtue of the reduced mechanical action of the paddle on an erodible formulation.

There thus exists a need to provide a dissolution testing vessel which overcomes this problem and allows the dissolution testing to be carried out on pharmaceutical formulations without any mechanical interaction between the formulation and the means used to agitate the medium in which the testing is being carried out. There is also required a means of assessing drug release from floating dosage forms without the sampling errors encountered when the dosage form is floating close to the surface of the dissolution medium.

Similarly, it would be useful to have dissolution testing apparatus which could be used to assess drug release reliably from a sinking, erodible, dosage form.

Thus, the present invention provides a dissolution testing vessel comprising means which prevent a formulation undergoing dissolution testing from floating freely at the surface of the testing medium, but which do not prevent the testing medium from moving freely within the vessel.

In a preferred embodiment, the means will also prevent a formulation undergoing dissolution testing from sinking to the bottom of the testing medium.

The invention therefore provides a testing vessel which will prevent the mechanical interaction with the means of agitation described above. In particular, the testing vessel of the invention is suitable for testing dissolution of both buoyant pharmaceutical formulations and sinking erodible dosage formulations.

Suitably, the means provided divide the vessel into at least two portions, while at the same time allowing the testing medium to move freely between those portions. In a preferred embodiment of the invention the means consists of an insert, which is provided as a mesh or grille and typically will have substantially the same diameter as that of the inner wall of the vessel. Suitably this can be made of stainless steel.

A particularly convenient way of allowing the insert to be held in place is to provide the vessel with one or more projections which project inwardly from the wall of

the vessel and on which the insert can rest.

Alternatively, a continuous projection can be provided which runs for substantially the whole of the inner circumference of the vessel, eg a collar, ridge or shoulder. Thus, the insert can simply be dropped into the interior of the vessel and will sit on the collar, ridge or shoulder.

Suitably, the one or more projections, or continuous projection respectively, can be formed as part of the vessel itself. This is particularly the case if the vessel is made of plastic or glass.

Therefore, in use, the pharmaceutical formulation under test will remain below the insert (if it is a floating dosage form) and will not be free to float at the surface. If, however, it is a sinking erodible dosage form, it can rest on the top of the insert. The medium itself is still agitated by means of a paddle or paddles and the normal aliquots can be taken at appropriate time points to determine the amount of active ingredient(s) released.

The mechanical interaction between the means, for example an insert, and the formulation, provides a suitable means of mechanical erosion, whether the dosage form is a floating type or sinking type, and therefore mimics the effect of the gastrointestinal tract *in vivo*. Unlike the paddle set to surface method described by Burns *et al*, 1995 (*supra*), there is little tendency for the formulation to stick to the means.

A preferred embodiment of the invention (used to assess

a floating dosage form) will now be described with reference to the accompanying drawing in which:

Figure 1: is a sectional view of a preferred embodiment of the invention.

In Figure 1 can be seen a sectional view of a preferred vessel(1) of the invention. The vessel(1) is moulded with a continuous indentation(2) which runs along the entire circumference of the vessel. This effectively divides the vessel into a lower portion(3), which represents approximately one third of the vessel's volume, and an upper portion(4). The provision of the indentation means that there is also provided a shoulder or ridge(5) which runs for the whole of the internal circumference of the vessel(1). An insert(6) is simply dropped into the vessel(1) and will rest upon the shoulder or ridge(5). A pharmaceutical formulation undergoing testing will be placed in the vessel before the insert(6) is dropped in and once the testing medium has been poured into the vessel the pharmaceutical formulation will remain within the lower portion(3) of the vessel(1) and will be prevented from floating freely at the surface of the testing medium by the insert(6).

EXAMPLE 1: Comparison of Modified and Existing Dissolution

A dissolution study was carried out with a floating dosage form, size '0' enteric-coated capsules containing a granule preparation of salmon calcitonin with a potency of 400 iu per capsule. The dissolution medium, volume 900 ml, was maintained at 37°C ± 1°C and contained 5.84 $g.l^{-1}$ disodium hydrogen orthophosphate, 4.61 $g.l^{-1}$

potassium dihydrogen orthophosphate, 2.00 $g.l^{-1}$ sodium cholate and 1.00 $g.l^{-1}$ sodium deoxycholate adjusted to pH 6.8. To determine the release of salmon calcitonin from the floating capsules, 5 ml samples of dissolution medium were removed for analysis. Samples were removed at specific intervals (eg 10, 15, 20, 25 min), up to 30 min, in each case the volume being replaced with fresh dissolution medium. The calcitonin content of the samples was determined by a specific ELISA for salmon calcitonin and quantified by comparison with authentic standards.

The two dissolution methods compared were as follows:

METHOD A - BP Type II apparatus with the paddles set to the surface of the dissolution medium as described by Burns *et al* (1995), *Int. J. Pharm.* (in press);

METHOD B - the present invention.

The paddle rotation speed in both cases was 100 rpm.

Results

The results of the study comparing the two dissolution methods are shown in Table 1.

TABLE 1

Time (min)	Standard Method A	Present Invention B
0	0	0
10	<2	<2
15	2.5 ± 27 (>200)	22 ± 19 (95)
20	20 ± 32 (160)	54 ± 21 (39)
25	50 ± 24 (48)	82 ± 7 (9)
30	73 ± 2 (3)	90 ± 8 (9)

The values are means of 6 determinations ± SD, with the coefficient of variance shown in brackets, and are expressed as percentage salmon calcitonin released from the dosage form.

The results in Table 1 show that the extent and rate of calcitonin release from a floating dosage form is considerably less than using the method described in the present invention. Another observation is the reduced variability in the measurements at each point with the present invention compared with the standard method illustrated by the lower coefficient of variance.

The skilled man will appreciate that any suitably shaped vessel can be used, of any suitable material. In addition, the means provided with the vessel for preventing the pharmaceutical formulation from floating freely at the surface of the testing medium can simply be adapted to the vessel shape. All such variations are intended to be within the scope of the present invention.

CLAIMS:

1. A dissolution testing vessel comprising means which prevent a formulation undergoing dissolution testing from floating freely at the surface of the testing medium, but which do not prevent the testing medium from moving freely within the vessel.

2. A dissolution testing vessel as claimed in claim 1 wherein the means comprises an insert.

3. A dissolution testing vessel as claimed in claim 2 wherein the insert has substantially the same diameter as the inner wall of the vessel.

4. A dissolution testing vessel as claimed in claim 2 or claim 3 wherein the insert consists of a mesh or grille.

5. A dissolution testing vessel as claimed in any one of claims 2 to 4 wherein the insert is made of stainless steel.

6. A dissolution testing vessel as claimed in any one of claims 1 to 5 wherein the vessel is provided with one or more projections projecting inwardly from the interior wall of the vessel.

7. A dissolution testing vessel as claimed in any one of claims 1 to 5 wherein the vessel is provided with a continuous projection, projecting inwardly from the interior wall of the vessel, which runs for substantially the whole of the inner circumference of the vessel.

8. A dissolution testing vessel as claimed in claim 6 or claim 7 wherein the one or more projections or continuous projection respectively are formed as part of the vessel itself.

9. A dissolution testing vessel as climed in any one of claims 1 to 8 which is constructed of glass or plastic.

10. A dissolution testing vessel as claimed in claim 1 which is for use with pharmaceutical formulations.

11. The use of a dissolution testing vessel as defined in any one of claims 1 to 10 in the dissolution testing of a pharmaceutical formulation.

12. A dissolution testing vessel as claimed in claim 1 substantially as hereinbefore described with reference to the accompanying drawings.

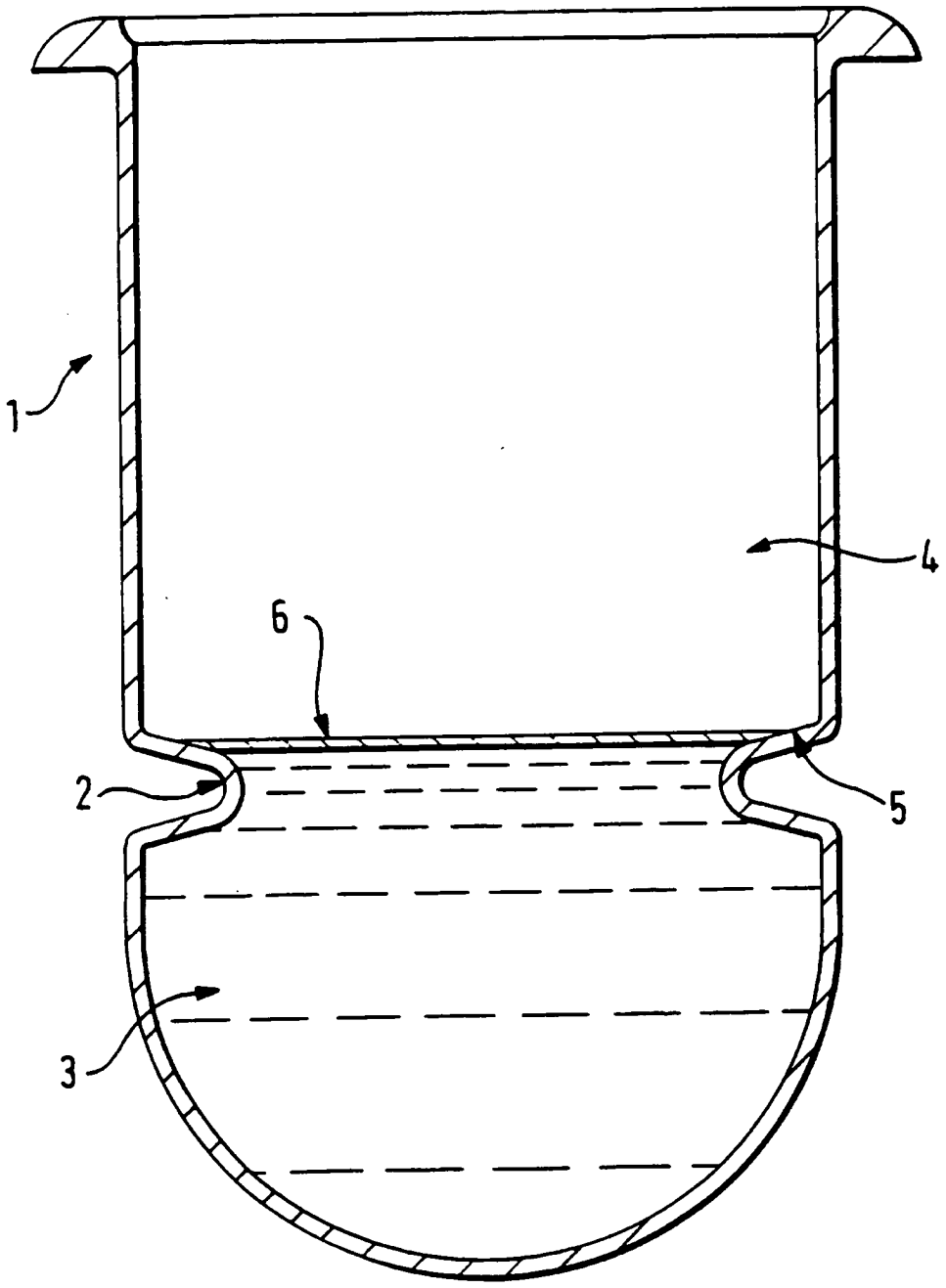


FIG. 1

INTERNATIONAL SEARCH REPORT

Inte. ɔnal Application No
PCT/GB 96/00493

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N13/00 G01N33/15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 546 628 (UNIV BORDEAUX) 30 November 1984 see page 4, line 29 - line 33; figures 1,4 ---	1-4,10, 11
X	US,A,4 681 858 (CHAUDHARI ATMA ET AL) 21 July 1987 see column 1, line 51 - line 53 see column 3, line 28 - column 4, line 20; figures ---	1,2,4,5, 10,11
X	WO,A,95 04923 (CIBA GEIGY AG ;SINNREICH JOEL (CH); BOSSHARD CHRISTIAN (CH)) 16 February 1995 see page 2, paragraph 2 see page 8, last paragraph - page 9, paragraph 2; figures see page 11, paragraph 1 --- -/--	1-4,9-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 1996	26.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Hocquet, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter .nal Application No
PCT/GB 96/00493

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 142 920 (BART GILLES ET AL) 1 September 1992 see column 1, line 45 - line 58 see column 5, line 1 - line 8 see column 5, line 62 - line 68; figure 2 see column 6, line 49 - line 54 ---	1-11
A	US,A,3 862 042 (AYRES WALDEMAR A) 21 January 1975 see column 3, line 23 - line 28; figures -----	7,8

1

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 96/00493

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2546628	30-11-84	NONE		
US-A-4681858	21-07-87	CA-A-	1274159	18-09-90
		GB-A,B	2191857	23-12-87
WO-A-9504923	16-02-95	AU-B-	7533494	28-02-95
		CA-A-	2167196	16-02-95
		EP-A-	0712490	22-05-96
US-A-5142920	01-09-92	FR-A-	2655874	21-06-91
		AT-T-	118702	15-03-95
		DE-D-	69017166	30-03-95
		DE-T-	69017166	14-06-95
		EP-A-	0434581	26-06-91
		ES-T-	2069723	16-05-95
		JP-A-	3229625	11-10-91
		JP-B-	7022691	15-03-95
US-A-3862042	21-01-75	NONE		